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Exposure to Elemental Carbon, Organic Carbon, Nitrate, and Sulfate Fractions of Fine Particulate Matter and Risk of Preterm Birth in New Jersey, Ohio, and Pennsylvania (2000–2005)

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Running title: Species of particulate matter and preterm birth

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Abstract

Background: Particulate matter ≤ 2.5 micrometers in aerodynamic diameter (PM_{2.5}) has been consistently associated with preterm birth (PTB) to varying degrees, but roles of PM_{2.5} species have been less studied.

Objective: We estimated risk differences (RD) of PTB (reported per 10⁶ pregnancies) associated with change in ambient concentrations of elemental carbon (EC), organic carbon (OC), nitrates (NO₃), and sulfates (SO₄).

Methods: From live birth certificates from three states, we constructed a cohort of singleton pregnancies at or beyond 20 weeks of gestation from 2000-2005 (n=1,771,225; 8% PTB). We estimated mean species exposures for each week of gestation from monitor-corrected Community Multi-Scale Air Quality modeling data. RDs and 95% confidence intervals (CI) for 4 PTB categories were estimated for each exposure using linear regression, adjusted for maternal race/ethnicity, marital status, education, age, smoking, maximum temperature, ozone, and season of conception. We also adjusted for other species in multi-species models.

Results: RDs varied by exposure window and outcome period. EC was positively associated with PTB after 27 and before 35 weeks of gestation. For example, for a 0.25 $\mu\text{g}/\text{m}^3$ increase in EC exposure during gestational week 9, RD = 96 (95% CI: -20, 213) and RD = 145 (95% CI: -50, 341) for PTB during weeks 28–31 and 32–34, respectively. Associations with OCs were null or negative. RDs for NO₃ were elevated with exposure in early weeks of gestation, and null in later weeks. RDs for SO₄ exposure were positively associated with PTB though magnitude varied across gestational weeks. We observed effect measure modification for associations between EC and PTB by race/ethnicity and smoking status.

Conclusion: EC and SO₄ may contribute to associations between PM_{2.5} and PTB. Associations varied according to the timing of exposure and the timing of PTB.

Introduction

Particulate matter ≤ 2.5 aerodynamic micrometers in diameter (PM_{2.5}), regulated under the Clean Air Act (42 U.S.C. § 7401) as a criteria air pollutant, is a complex mixture of extremely small particles and liquid droplets. Chemical composition of PM_{2.5} varies spatially and temporally (Bell et al. 2007), as do strength of associations between PM and various health effects (Franklin et al. 2007); these variations in health effects and compositions may reflect differing toxicity of PM species. PM_{2.5} exposure has been studied with many health outcomes, among them preterm birth (PTB). PTB is a marker for fetal underdevelopment and a risk factor for further poor health outcomes (Butler and Behrman 2007; Saigal and Doyle 2008).

While most studies of PM_{2.5} and PTB use PM_{2.5} mass as the exposure metric due to limited speciated data, four studies have examined associations between PM_{2.5} species and PTB (Brauer et al. 2008; Darrow et al. 2009; Gehring et al. 2011; Wilhelm et al. 2011). These studies have found elevations in risk or odds of PTB associated with exposure to PM_{2.5} species: elemental carbon (EC), nitrate (NO₃), sulfate (SO₄), and organic carbon (OC). However, null or inverse risks/odds have also been observed for these chemicals depending on study type or window of exposure examined. Two studies that examined a close corollary of EC (black carbon/soot) lacked continuous EC monitoring data for use in land-use regression models (LUR); therefore used PM monitoring data to adjust for temporal fluctuations (Brauer et al. 2008; Gehring et al. 2011). Darrow et al. (2009) examined a number of different species but used a single monitoring location. Because all studies depended on monitoring data, study samples were limited to areas with monitors. Despite sparse data on relationships between PM_{2.5} species and PTB, there is

some evidence that certain species, e.g., sulfates or nitrates, may be more influential than others (Darrow et al. 2009; Wilhelm et al. 2011).

Objectives

This study builds upon previous research to examine chemical components of PM_{2.5} in relation to PTB by investigating a large study area with a wide range of PM_{2.5} levels and investigating multiple species and exposure periods. We examine associations between ambient EC, OC, SO₄, and NO₃ and risk of PTB using a cohort of pregnancies reaching 20 weeks of gestation from singleton live births across six years and three states (Pennsylvania (PA), Ohio (OH), and New Jersey (NJ)), selected for exposure variability as they contain areas of high and low PM_{2.5} concentration. We employ the EPA's Community Multiscale Air Quality (CMAQ) model (Hogrefe et al. 2009), which offers complete spatial coverage and daily estimated air pollutant concentrations. We estimate risk differences (RD (95% Confidence Interval)) for 1 µg/m³ increases in average weekly OC, NO₃, and SO₄ exposures, and 0.25 µg/m³ for EC at each week of gestation and birth at four categories of preterm gestation.

Methods

Methods are described in detail elsewhere (Rappazzo et al. 2014). Briefly, the study population was generated from live birth records provided by State Health Departments of PA, NJ, and OH. The population was restricted to singleton births with geocodable addresses and gestational age data, and no recorded birth defects. To ensure that each pregnancy was entirely observable within the study period and avoid fixed-cohort bias (Strand et al. 2011), eligible pregnancies had to have achieved gestational week 20 no earlier than 1 January 2000 and gestational week 45 no

later than 31 December 2005. From all birth records (n=2,495,350) these restrictions led to a population of 1,940,213 pregnancies. For analysis, the population was further restricted to those with complete covariate information (n=1,771,255).

Gestational age was determined by clinical estimate of gestation (CEG) as reported on birth certificates. To better elucidate severity of preterm birth and determine if associations between preterm birth and PM_{2.5} species vary according to gestational age, PTBs were divided into four categories based on World Health Organization definitions (WHO 2013): extremely PTB (ExPTB) gestational age between 20-27 weeks; very PTB (VPTB) gestational age 28-31 weeks; moderate PTB (MPTB) gestational age 32-34 weeks; and late PTB (LPTB) gestational age 35-36 weeks. Term births were between 37-45 completed gestational weeks.

Daily estimated concentrations of PM_{2.5} species (EC, OC, NO₃, SO₄) were provided by the EPA's Atmospheric Exposure Integration Branch for 1999 to 2005 in 12 km grids. These estimates were constructed by Hogrefe et al. (2009) using output from CMAQ bias-corrected with monitoring network data. Briefly, meteorological conditions and criteria pollutant emissions are input into CMAQ, which simulates atmospheric processes and estimates gridded concentrations of ambient air pollutants; grids were matched to monitoring sites and a filter applied to created baseline concentrations of PM_{2.5} species (Hogrefe et al. 2009). Adjustment factors were created (ratio of observed to modeled concentrations), spatially interpolated across the grids, and multiplied by CMAQ output to produce bias-corrected concentrations (Hogrefe et al. 2009). Maternal addresses at birth were geocoded using the ZP4 address locator program (Semaphore Corporation, Monterey, CA) and the ArcGIS online geocoding service in ArcMap

10 (ESRI, Redlands, CA). We matched addresses to CMAQ grid and concentration estimates for each day of pregnancy. Date of last menstrual period was used as “start of pregnancy” and estimated using CEG and date of birth. Exposures were averaged over fixed seven day periods to estimate weekly average concentrations (i.e., average of days 1-7 equals concentration for week 1, average of days 8-14 equals concentration for week 2, etc.) for all pregnancies.

We identified potential confounders a priori based on previous literature and knowledge of factors influencing PTB and air pollution (Brauer et al. 2008; Butler and Behrman 2007; Darrow et al. 2009; Gehring et al. 2011; Knüppel and Stang 2010; Wilhelm et al. 2011). From birth certificate, we included: maternal race/ethnicity (non-Hispanic white, non-Hispanic black, hispanic, other) education (<8th grade, some high school, high school diploma, some college, bachelor’s degree, graduate school), marital status, age at delivery (3-knot restricted quadratic spline), smoking status, and season of conception (Summer = June-August; Fall = September-November; Winter = December- February; Spring = March-May); from CMAQ we included maximum temperature (continuous, averaged daily values) and ozone concentration (continuous, averaged daily values), which has been associated with PTB and co-occurs with PM_{2.5} (Lee et al. 2013). Potential effect measure modifiers/modification (EMM) identified a priori included race/ethnicity (black non-Hispanic, non-black), smoking status (smoker, non-smoker), infant sex (male, female), and maternal parity (primiparous, multiparous). When EMM was observed (interaction terms with significance at $p < 0.05$) both marginal and stratified effect estimates are presented, as marginal effect estimates effectively standardized to population distributions reflect overall associations with PM_{2.5} species, while stratified effect estimates highlight potentially vulnerable subgroups for targeted intervention.

RDs were estimated using modified Poisson regression with an identity link; Poisson models produce equally valid estimates as binomial models; though Poisson models are less efficient than binomial models, they are less likely to result in nonconvergence (Spiegelman and Hertzmark 2005; Wacholder 1986; Zou 2004). In lieu of testing null hypotheses ($RD = 0$), we examined patterns of RD estimates and focused on their precision, thereby not raising multiple testing concerns. We estimated absolute effect measures because they, with outcome severity, are informative for public health impact and decision making. RDs are interpreted as change in PTB per 1,000,000 pregnancies for every one unit increase in species concentration. Number needed to treat ($NNT = 1/RD$) may also be calculated from RDs (Laupacis et al. 1988); NNT has a simple interpretation and improves risk communication. We used an at-risk approach in our models; all births that could have experienced birth at the weeks of interest were included in the model. For example, very preterm births (births at 28–31 weeks) were included in models of associations with extremely preterm births (births at 20–17 weeks), but extremely preterm births were not included in models of very preterm, as they were not at risk of birth at 28–31 weeks.. $PM_{2.5}$ species were modeled as continuous variables, linearity of outcome-exposure associations was examined using various coding methods (e.g., categories based on percentiles) and found to be generally linear; models using categories of species exposure were monotonic increasing or decreasing (data not shown). Exposure contrasts were set at $1 \mu g/m^3$ for species with an interquartile range of greater than 1 (OC, NO_3 , SO_4) or at $0.25 \mu g/m^3$ (EC). Each species was evaluated in a single-species model and a multi-species model with all $PM_{2.5}$ species. For comparability with previous work, we examined exposures averaged by trimester and entire pregnancy period. All statistical analyses were performed using SAS version 9.3 (Cary, NC).

This research was approved by the University of North Carolina at Chapel Hill's Office of Human Research Ethics, Pennsylvania Department of Health Bureau of Health Statistics & Research, New Jersey Department of Health and Senior Services Institutional Review Board, and the Ohio Department of Health Human Subjects Institutional Review Board.

Results

A total of 1,771,255 pregnancies (out of potential 1,940,212) were included in adjusted analysis as they had complete covariate information. Of these, 140,987 (8%) were PTBs. Women with PTB, compared to term births, had lower educational attainment, were more often unmarried, and were more likely to be non-Hispanic black (Table 1). The study population was primarily urban, with 80% in the highest rural-urban continuum code (USDA 2013). Women in the risk set excluded due to non-geocodable addresses were more likely to be younger, white, unmarried, have lower educational attainment, and have a PTB (~9% v. 8% in analytic population) than included women. Of the women excluded due to missing covariate information 7% were missing maternal age, while other covariates had low proportions of missing values (~1% or less). Proportions of missing observations were similar across PTB categories for most covariates, though maternal education and smoking status had higher proportions of missings in the ExPTB group compared to other categories (e.g., smoking status missing 3% in ExPTB group vs. 1% in others).

Average weekly pollutant concentrations were similar across categories of PTB (Supplemental Material, Table S.1). Temporal correlation coefficients ranged from: 0.76 to 0.50 for EC; 0.75 to 0 for OC; 0.70 to -0.45 for NO₃; and 0.64 to -0.45 for SO₄. Correlations between species were

high for EC-OC (~ 0.80) and OC-NO₃ (~ 0.59) and moderate for EC-NO₃ (~ 0.38), OC-SO₄ (~ -0.21), and NO₃-SO₄ (~ -0.43). EC and SO₄ were not correlated (~ -0.07).

PTB RDs associated with a $0.25\mu\text{g}/\text{m}^3$ increase in EC, with exposure at each week of gestation, are shown in Figure 1. For EC exposure, ExPTB RDs were null for exposure at all gestational weeks, with similar estimates from single- and multi-species models. For VPTB, single-species model RDs were slightly elevated at some points in mid pregnancy, though many weeks were near null. However, EC RDs were generally higher in multi-species models. For MPTB, single-species RDs were elevated with exposure to EC at gestational weeks 4 and 5, and consistently positive from week 7 through week 21. Multi-species model RDs were positive for exposures in weeks 1-21, and higher than corresponding RDs from the single-species models. For LPTB, RDs from single-species models were consistently negative or null, whereas EC RDs from multi-species models were positive for exposures during weeks 1-24.

PTB RDs for a $1\mu\text{g}/\text{m}^3$ increase in OC with exposures at each week of gestation are shown in Figure 2. In single and multi-species models associations of OC were generally null for ExPTB. For VPTB, OC RDs were generally null in single-species models, but were negative in multi-species models. For MPTB, single-species RDs were null, while multi-species RDs were negative for exposures in weeks 1-27. For LPTB, single-species RDs were negative for exposures across all weeks of gestation. In multi-species models, OC RDs were more negative than in single-species models for exposures at weeks 1-25, after which RDs were similar to those observed in single-species models.

PTB RDs for a $1\mu\text{g}/\text{m}^3$ increase in NO_3 with exposures at each week of gestation are shown in Figure 3. For NO_3 exposure, both single and multi-species, RDs for ExPTB were consistently elevated at gestational weeks 1-11 then near null or negative. For VPTB, single-species associations were elevated for exposure in weeks 3-10, then sporadically positive over later weeks; multi-species RDs were similar to single-species RDs. For MPTB and LPTB, single-species RDs were generally null or slightly elevated in early weeks, and null afterwards with some negative risks at the latest weeks. With multi-species models, RDs for NO_3 were similar to single-species associations for MPTB, but became more positive for LPTB, particularly in earlier weeks of exposure.

PTB RDs for a $1\mu\text{g}/\text{m}^3$ increase in SO_4 with exposures at each week of gestation are shown in Figure 4. For SO_4 exposure in single species models, ExPTB exhibits positive RDs before week 7 and after week 13, with null associations for weeks 8-12; multi-species model RDs were similar to single-species model RDs. RDs for VPTB, MPTB, and LPTB were generally elevated across all weeks of gestation in single and multi-species models.

No EMM (interaction term $p < 0.05$) was observed for any species by infant sex or maternal parity, data not shown. RDs for EC exposure and VPTB, MPTB, and LPTB were higher than would be expected on an additive scale for women of black race/ethnicity and women who smoked during pregnancy (Figure 5). There was evidence for modification of effect estimates for OC exposures with race/ethnicity and smoking status, following similar patterns for EC estimates (Supplemental Material, Figure S.1). However, EMM for OC was less consistent across exposure categories than EMM for EC; where interaction terms met criteria at most or all

weeks of exposure for EC, there was considerable variation in OC interaction terms across exposure weeks and outcome groups. For NO₃, potential EMM was observed only for maternal smoking status in LPTB outcomes with exposure in early gestation (Supplemental Material, Figure S.2). There was limited to no evidence for EMM for SO₄ exposures (Supplemental Material, Figure S.3).

For trimester and pregnancy exposures, associations were generally positive for NO₃ and SO₄ and negative for OC across exposure windows, while associations with EC were generally positive for 1st trimester and negative for entire pregnancy windows (Supplemental Material, Table S.2). Third trimester and entire pregnancy exposures should be interpreted with caution as length of exposure period varies based on gestational age.

Discussion

We found PTB risk associated with PM_{2.5} varies by species, with potential for different associations at early vs. late PTB and during different windows of exposure. EC had the strongest associations in VPTB and MPTB, particularly with exposure windows before the 23rd week of gestation and across single and multi-species models. Associations for EC and LPTB diverged between single and multi-species models, with negative RDs in single-species models and positive RDs in multi-species models. EC also demonstrated EMM with race/ethnicity (black non-Hispanic v. non-black) and smoking status wherein RDs among black women were higher than among non-black women, with smoking status following similar patterns. We observed negative RDs with OC but only in LPTB or multi-species models. As it is unlikely OCs have a protective health effect, this may be due to model error (e.g., in multi-species models

where EC has a higher association, OC has a lower association, possibly an artifact of high correlation). It is also possible that due to correlation, the presence of both EC and OC in models creates a sparse data problem. If so, we would expect to see associations moving drastically away from the null, leading to biased RDs and interpretations. However, these drastic shifts do not seem to be the case for EC and OC RDs in our analysis. Other potential explanations for negative RDs observed include interactions between EC and OC, and non-linear associations. NO₃ was associated with increased RDs of PTB with exposures in weeks of the 1st trimester with earlier PTB categories. SO₄ shows increased RDs for PTB across categories of gestation and with most exposure windows. SO₄ appears to have a role in risk of PTB, though no particular windows of vulnerability emerged from our analysis.

Though mechanisms of action for PM_{2.5} species on PTB are poorly understood at present, likely contenders are inflammatory or oxidative stress processes. PM_{2.5} exposure has been linked to increased markers of systemic inflammation in humans and changes in placental morphology in mice, which may be a consequence of inflammation (Backes et al. 2013; Veras et al. 2008). Changes in the placenta may lead to inadequate placental perfusion or impaired nutrient exchange (Kannan et al. 2006). Inflammation may also lead to the creation of reactive oxygen species, which can cause cell damage, DNA damage, disruption of cellular processes, irreversible protein modifications, or alternations in cellular signaling (U.S. EPA 2009). It is not known if these processes would lead to PTB, however they are alterations of normal function and may disrupt normal processes of gestation.

Each species has properties that may cause harm, though again these pathways are poorly understood for pregnancy outcomes. EC may directly induce a health response or may bear other toxic chemicals that induce inflammation (Ritz and Wilhelm 2008). EMM observed with race/ethnicity and smoking status may indicate priming (an initial insult that makes a secondary insult more effective) by exposure to the pollutants in cigarette smoke and the social stressors we believe race/ethnicity represents. Associations observed with OC exposures should be interpreted with caution, as the modeling of OCs is restricted to primary OC, which is directly emitted to the atmosphere from a source. Secondary OC, formed by atmospheric reactions during transport, can comprise a substantial fraction of OC mass (U.S. EPA 2009), but was not included in the CMAQ model used in our analysis due to uncertainties with estimating the fraction using chemical transport models. This gives the OC concentrations an unexpectedly high correlation with EC (which is formed only through primary processes), and associations may be unduly influenced by this correlation. The epidemiologic and toxicological literature lacks discussion of the role of NO_3 and SO_4 on birth outcomes. However, some possibilities may be extrapolated from other literature indicating that they mediate inflammatory processes (Bind et al. 2012). The area of $\text{PM}_{2.5}$ species and PTB has received limited attention, though it is likely that toxicity of $\text{PM}_{2.5}$ species influence $\text{PM}_{2.5}$'s effects on PTB.

To our knowledge, no other studies of $\text{PM}_{2.5}$ species have examined EMM. We believe our finding of high RDs for women of black race/ethnicity compared to non-black women is not likely to be a biological effect of race/ethnicity, but rather a priming effect of factors that race/ethnicity represents (e.g., stress due to institutionalized racism (Jones 2000; Nuru-Jeter et al. 2009)). In this situation such factors would deplete women's resources for dealing with EC

insults, therefore EC would have a worse impact on health. In other words, social stressors related to race/ethnicity in the United States may create an “allostatic load” in which a woman has long term biological dysregulation due to continuous or frequently occurring presence of stressors (McEwen and Seeman 1999). This then prevents women from responding biologically appropriately to further stressors including air pollutants. Smoking may work in a similar, though more direct manner. Particulates in cigarette smoke offer an initial insult, which may overwhelm a woman’s protective/coping processes, and EC exposure adds an additional insult that then has fewer barriers to adverse effects. These pathways are plausible, but there has been little research on this topic.

Currently, four studies are published on the influence of PM_{2.5} species on PTB, with a variety of study designs, exposures, and exposure assessments between them (Brauer et al. 2008; Darrow et al. 2009; Gehring et al. 2011; Wilhelm et al. 2011). Two studies used LUR methods to estimate soot or black carbon exposures. Brauer et al. (2008) found no association of black carbon with entire pregnancy exposures, while Gehring et al. (2011) found positive odds ratios with entire pregnancy and last month exposures. As Brauer et al. (2008) recount in their study, LUR model performed poorly in evaluation tests and used PM_{2.5} data for temporal adjustment, as only annual black carbon data was available. As reported in their publication, Gehring et al. (2011) did not account for spatial variation of soot/PM_{2.5} between 1999/2000, years when the environmental data were available, and 1996/97, years when pregnancies were studied. Our study shares a cohort study design with these studies but uses different exposure assessment methods. While the LUR models offered advantages in detection of spatial heterogeneity of air pollutants, our use of bias-corrected CMAQ model offered other benefits. Our study was large and included a broad

population, and did not need to be limited to a monitor rich area. Our CMAQ model was also constructed using data covering the entirety of pregnancies in our study population.

Two further studies each examined a variety of PM_{2.5} species. In a time-series study of the Atlanta area, Darrow et al. (2009) estimated positive risk ratios for NO₃ and SO₄ with exposure in the 1st month of pregnancy and for SO₄ and EC with a 1 week lag from birth. OCs had null RDs for all exposure windows examined. Given differences in study design and exposure assessment (use of a single monitor for PM_{2.5} species ascertainment), our results are fairly congruent with the results from Darrow et al. (2009). Differences between results do occur; for example, with EC exposures in early pregnancy we found elevated RDs, though not for all PTB categories. Wilhelm et al. (2011) used a case-control design with entire pregnancy exposures and found elevated odds ratios with EC, OC, and ammonium nitrate exposure in single-species models and ammonium nitrate in multi-species models. Odds ratios were null for ammonium sulfate in single-species models and inverse in multi-species models. Wilhelm et al.'s (2011) use of a dense monitoring network for species analyses may better characterize PM_{2.5} species spatial heterogeneity than CMAQ models. Wilhelm et al. (2011) reported on whole pregnancy exposure due to limited temporal variation in exposure, whereas we were able to examine weekly exposure windows throughout pregnancy. This investigation allowed us to examine associations with exposure at each specific week of gestation, which may help identify the most relevant exposure time windows for targeted mechanistic research.

Our study also diverges from previous literature with examination of EMM, RD as the measures of effect, and use of refined PTB categories. Broadly defined, PTB captures a 4 month period across pregnancy wherein development occurs rapidly. By examining more refined categories of PTB, rather than a single outcome, we investigate associations specific to each gestational age. The etiology of PTB may vary by gestational week, as fetal development and vulnerabilities shift rapidly across the 4 month period comprising PTB. Our analysis supported this, as we observed different associations based on PTB category, which collapsing PTB into one category may have masked.

In order to better inform both etiology and policy research, we took advantage of our large population to examine potential EMM, providing insight into possible vulnerable populations. Estimating NNTs for risk communication is also a simple endeavor. For example, at week 5 of gestation NNTs for EC and VPTB correspond to 8936 for non-black and 1970 for black women; meaning for every $0.25\mu\text{g}/\text{m}^3$ increase in ambient EC concentrations for 8936 non-black or 1970 black pregnant women 1 VPTB occurs (assuming causality). For public health regulatory processes to work best, understanding of risk for both the aggregate and vulnerable subpopulations is needed.

As with many studies of air pollution, classification of exposure is imperfect. Even with bias correction, the models used to estimate pollutant concentrations are limited. This is particularly true with $\text{PM}_{2.5}$ species, for which monitoring remains sparse, and monitoring of particular species may be inconsistent across sites. For example, CMAQ models (uncorrected) are known to underperform for prediction of OC concentrations; bias correction can improve OC estimates,

but high uncertainty for predictions remains as the distance between monitors is large and the same measurement methods are not used at all sites (Hogrefe et al. 2009). In addition, the 12km grids used here will smooth over important intra-urban variation in exposure. Secondary pollutants such as NO_3 and SO_4 are typically well correlated on a regional scale, while EC is more spatially diverse with most impacts near combustion sources. While all models have performance issues to some degree, the concentration estimates produced by CMAQ models allow for the estimation of health effects across large areas/populations, whereas the use of only monitoring networks is much more constrained to regions geographically close to monitors. Beyond limitations specific to the use of models, potential exposure classification issues include: use of ambient rather than personal measures of $\text{PM}_{2.5}$ species and using a single residential point for exposure assignment rather than a profile of where a woman's time is spent – including indoor versus outdoor exposure and the assumption that women had a single residence throughout pregnancy. Though these factors are likely non-differential by outcome, their consequences may be complicated, leading to responses that may be biased toward or away from the null depending on if estimated exposures were lower or higher than true exposures, or if these factors are differential by confounders such as SES. While having individual level exposures would be beneficial, we can interpret the observed results as estimated effects of ambient exposures, which are most likely to be affected by changes to air pollution regulations. This study identified associations between average weekly exposure to EC, OC, NO_3 , and SO_4 during gestation and risk of four categories of PTB for women residing in OH, PA, or NJ from 2000 to 2005. EC and SO_4 , among the best characterized of the $\text{PM}_{2.5}$ species, had the most consistent associations with risk of PTB in both single-and multi-species models. Differences

existed not only between PM_{2.5} species, but also with different windows of exposure and PTB at specific gestational ages. These results suggest diverse periods of action for the species of PM, along with differing windows of vulnerability for various categories of PTB. Growth in our understanding of these complex relations will require future studies of particulate matter and its components to incorporate careful assessment of exposure timing and refined definitions of preterm gestational age.

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Table 1. Maternal and fetal characteristics across term and preterm categories for included pregnancies to women living in OH, PA, or NJ 2000-2005 [n (%)].

Characteristic	ExPTB	VPTB	MPTB	LPTB	Term births
Observations (n)	8532	11885	31168	89402	1630268
Maternal Education					
Grad school	542 (6)	927 (8)	2,855 (9)	9,194 (10)	202,082 (12)
BA	1,012 (12)	1,634 (14)	4,666 (15)	14,906 (17)	324,400 (20)
College	1,873 (22)	2,584 (22)	6,934 (22)	20,283 (23)	370,746 (23)
HS	3,172 (37)	4,182 (35)	10,670 (34)	29,357 (33)	488,712 (30)
Some HS	1,632 (19)	2,174 (18)	4,980 (16)	12,768 (14)	183,974 (11)
<8th grade	301 (4)	384 (3)	1,063 (3)	2,894 (3)	60,354 (4)
Maternal Race/Ethnicity					
Non-Hispanic White	4,070 (48)	6,509 (55)	18,738 (60)	58,540 (65)	1,147,612 (70)
Non-Hispanic Black	3,211 (38)	3,611 (30)	7,635 (24)	16,815 (19)	222,892 (14)
Hispanic	997 (12)	1,321 (11)	3,417 (11)	9,935 (11)	176,621 (11)
Other	254 (3)	444 (4)	1,378 (4)	4,112 (5)	83,143 (5)
Maternal Age at Delivery					
<15	124 (1)	138 (1)	282 (1)	629 (1)	7,935 (<1)
15-19	1,207 (14)	1,397 (12)	3,213 (10)	8,412 (9)	130,052 (8)
20-24	2,088 (24)	2,765 (23)	7,107 (23)	20,052 (22)	350,059 (21)
25-29	1,997 (23)	2,746 (23)	7,513 (24)	22,912 (26)	436,453 (27)
30-34	1,814 (21)	2,785 (23)	7,522 (24)	22,447 (25)	444,216 (27)
35-39	1,030 (12)	1,615 (14)	4,362 (14)	11,988 (13)	217,260 (13)
40-44	254 (3)	415 (3)	1,100 (4)	2,790 (3)	42,480 (3)
45+	18 (<1)	24 (<1)	69 (<1)	172 (<1)	1,813 (<1)
Marital Status					
Married	3,844 (45)	6,010 (51)	17,395 (56)	55,307 (62)	1,113,352 (68)
Single	4,688 (55)	5,875 (49)	13,773 (44)	34,095 (38)	516,916 (32)
Maternal Smoking Status					
No	6,639 (78)	9,219 (78)	24,446 (78)	72,374 (81)	1,385,050 (85)
Yes	1,893 (22)	2,669 (22)	6,722 (22)	17,028 (19)	245,218 (15)
Infant Sex					
Male	4,460 (52)	6,314 (53)	16,638 (53)	47,666 (53)	830,821 (51)
Female	4,068 (48)	5,571 (47)	14,529 (47)	41,735 (47)	799,432 (49)
Missing	4 (0)	0 (0)	1 (0)	1 (0)	15 (0)
Season of Conception					
Summer	1,952 (23)	2,816 (24)	7,224 (23)	20,904 (23)	385,555 (24)
Fall	2,324 (27)	3,269 (28)	8,688 (28)	24,703 (28)	457,486 (28)
Winter	2,316 (27)	3,193 (27)	8,360 (27)	23,999 (27)	436,947 (27)
Spring	1,940 (23)	2,607 (22)	6,896 (22)	19,796 (22)	350,280 (21)
Parity					
Primiparous	4,291 (50)	5,671 (48)	14,168 (45)	37,373 (42)	651,940 (40)
Multiparous	4,196 (49)	6,156 (52)	16,875 (54)	51,768 (58)	974,242 (60)
Missing	45 (1)	58 (0)	125 (0)	261 (0)	4,086 (0)

Figure Legends

Figure 1: Risk differences per 1,000,000 pregnancies for 0.25 $\mu\text{g}/\text{m}^3$ increases in EC. Single-species models adjusted for maternal education, race/ethnicity, marital status, age at delivery, smoking, season of conception, maximum temperature, and O₃. Multi-species models are also adjusted for OC, NO₃, and SO₄. ExPTB: birth at 20-27 weeks, VPTB: birth at 28-31 weeks, MPTB: birth at 32-34 weeks, and LPTB: birth at 35-36 weeks of gestation.

Figure 2: Risk differences per 1,000,000 pregnancies for 1 $\mu\text{g}/\text{m}^3$ increases in OC. Single-species models adjusted for maternal education, race/ethnicity, marital status, age at delivery, smoking, season of conception, maximum temperature, and O₃. Multi-species models are also adjusted for OC, NO₃, and SO₄. ExPTB: birth at 20-27 weeks, VPTB: birth at 28-31 weeks, MPTB: birth at 32-34 weeks, and LPTB: birth at 35-36 weeks of gestation.

Figure 3: Risk differences per 1,000,000 pregnancies for 1 $\mu\text{g}/\text{m}^3$ increases in NO₃. Single-species models adjusted for maternal education, race/ethnicity, marital status, age at delivery, smoking, season of conception, maximum temperature, and O₃. Multi-species models are also adjusted for OC, NO₃, and SO₄. ExPTB: birth at 20-27 weeks, VPTB: birth at 28-31 weeks, MPTB: birth at 32-34 weeks, and LPTB: birth at 35-36 weeks of gestation.

Figure 4: Risk differences per 1,000,000 pregnancies for 1 $\mu\text{g}/\text{m}^3$ increases in SO₄. Single-species models adjusted for maternal education, race/ethnicity, marital status, age at delivery, smoking, season of conception, maximum temperature, and O₃. Multi-species models are also adjusted for OC, NO₃, and SO₄. ExPTB: birth at 20-27 weeks, VPTB: birth at 28-31 weeks, MPTB: birth at 32-34 weeks, and LPTB: birth at 35-36 weeks of gestation.

Figure 5: Effect measure modification by black race/ethnicity (left) and smoking status (right) for elemental carbon. Models adjusted for maternal education level, marital status, age at delivery, smoking status (race/ethnicity models), race/ethnicity (smoking status models), season of conception, maximum temperature and co-occurring ozone. ExPTB: birth at 20-27 weeks, VPTB: birth at 28-31 weeks, MPTB: birth at 32-34 weeks, and LPTB: birth at 35-36 weeks of gestation. Weeks where interaction terms have $p < 0.05$ are: ExPTB: none; VPTB: all; MPTB: all; LPTB: all.

Figure 1.

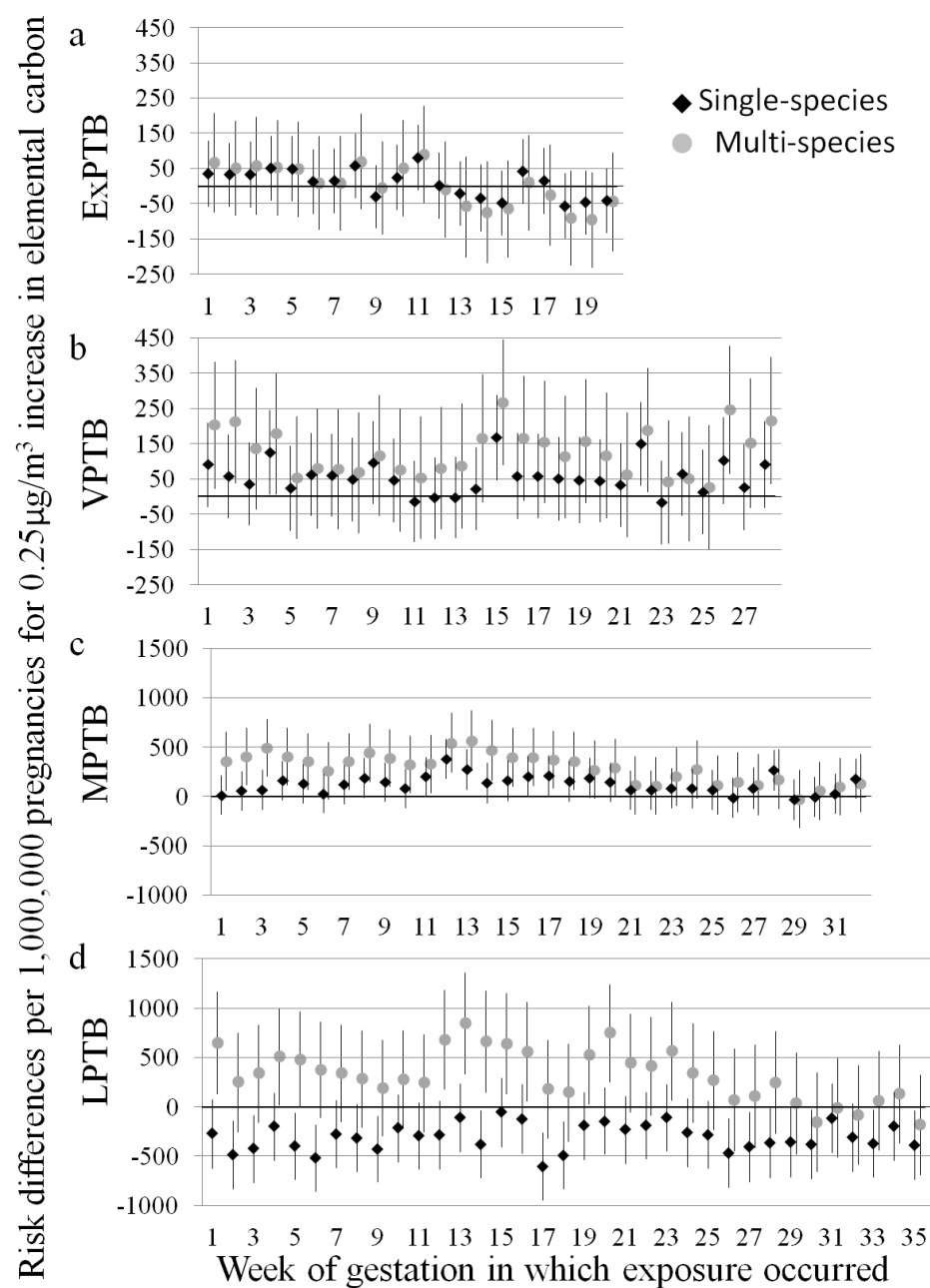


Figure 2.

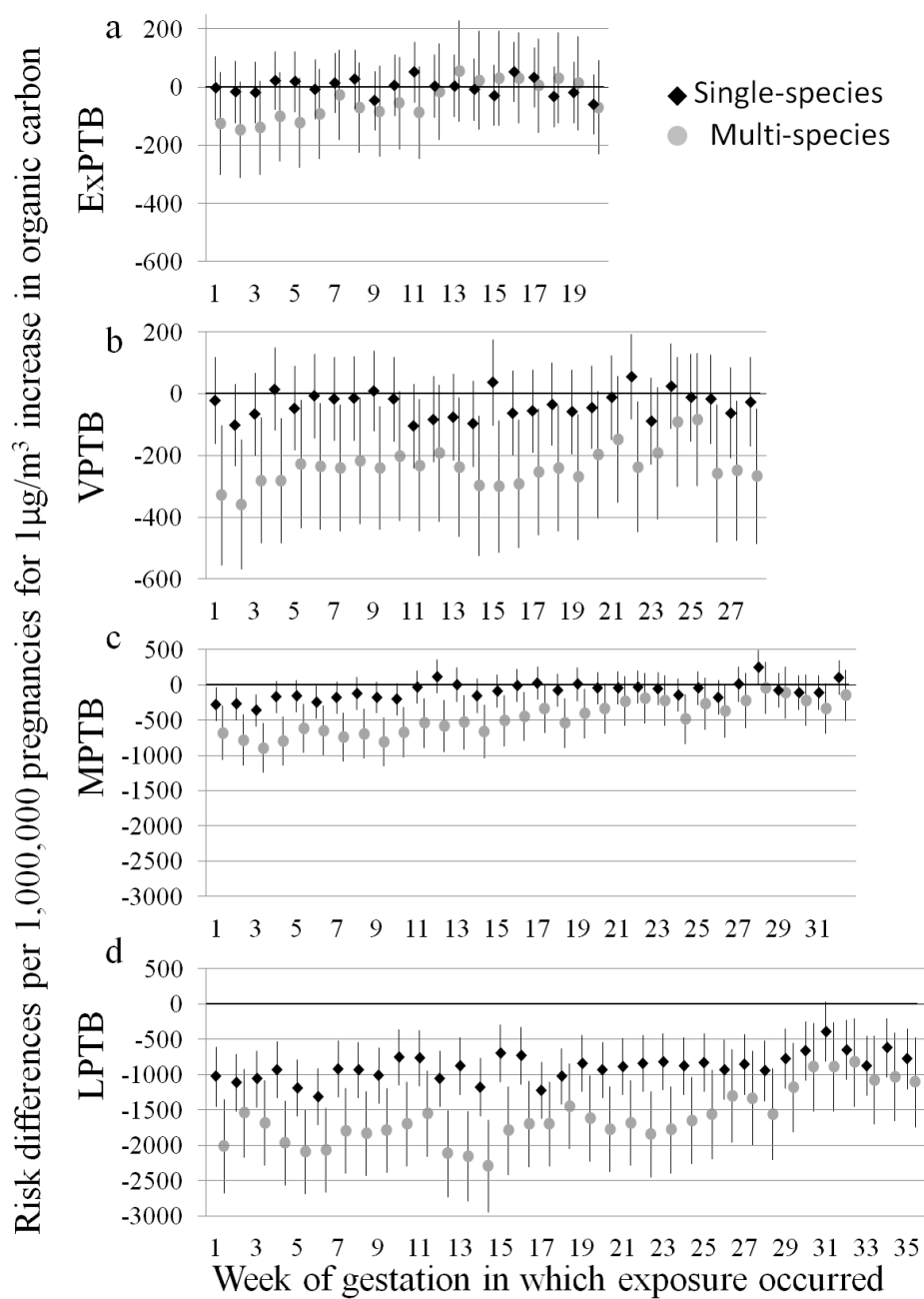


Figure 3.

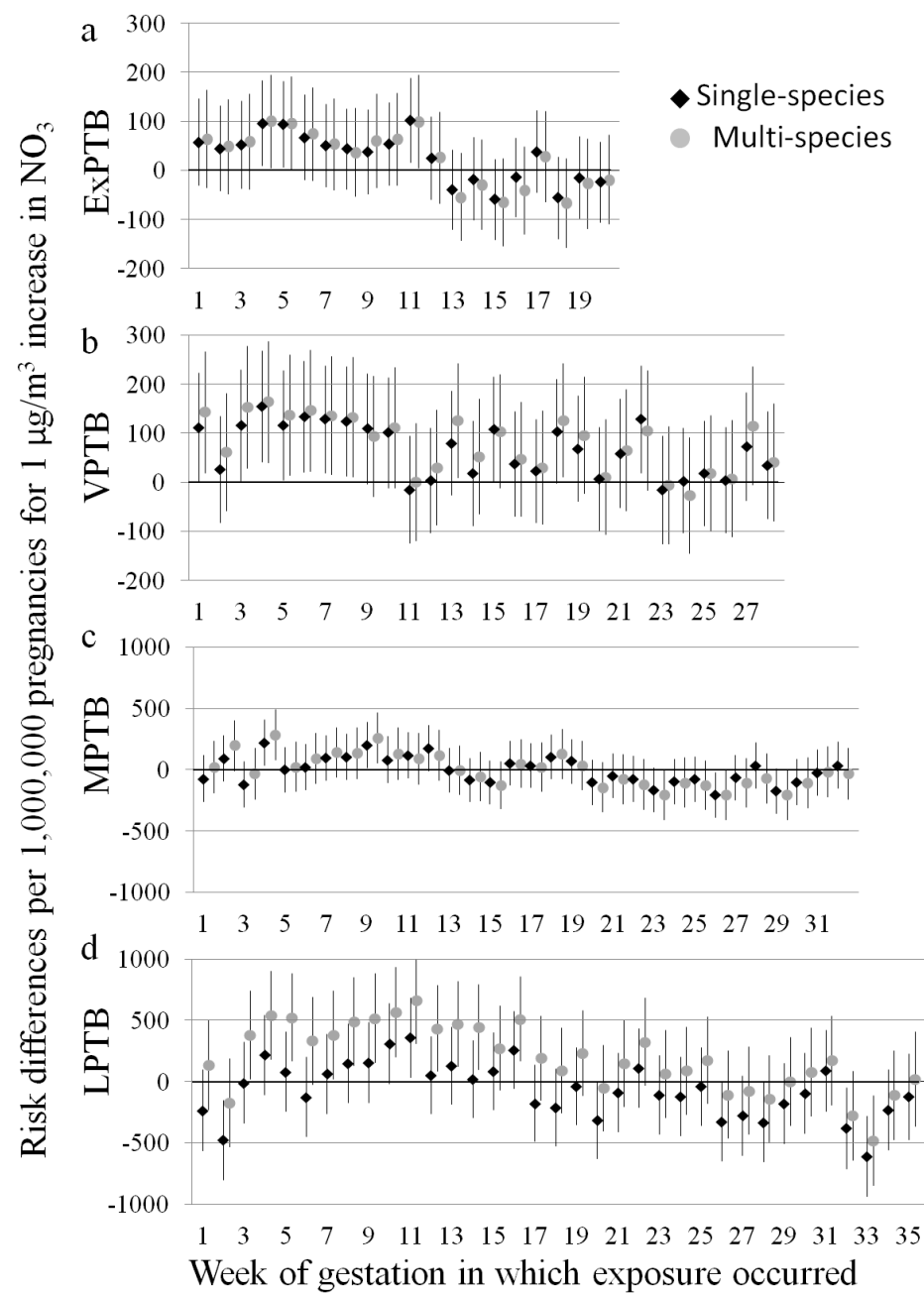


Figure 4.

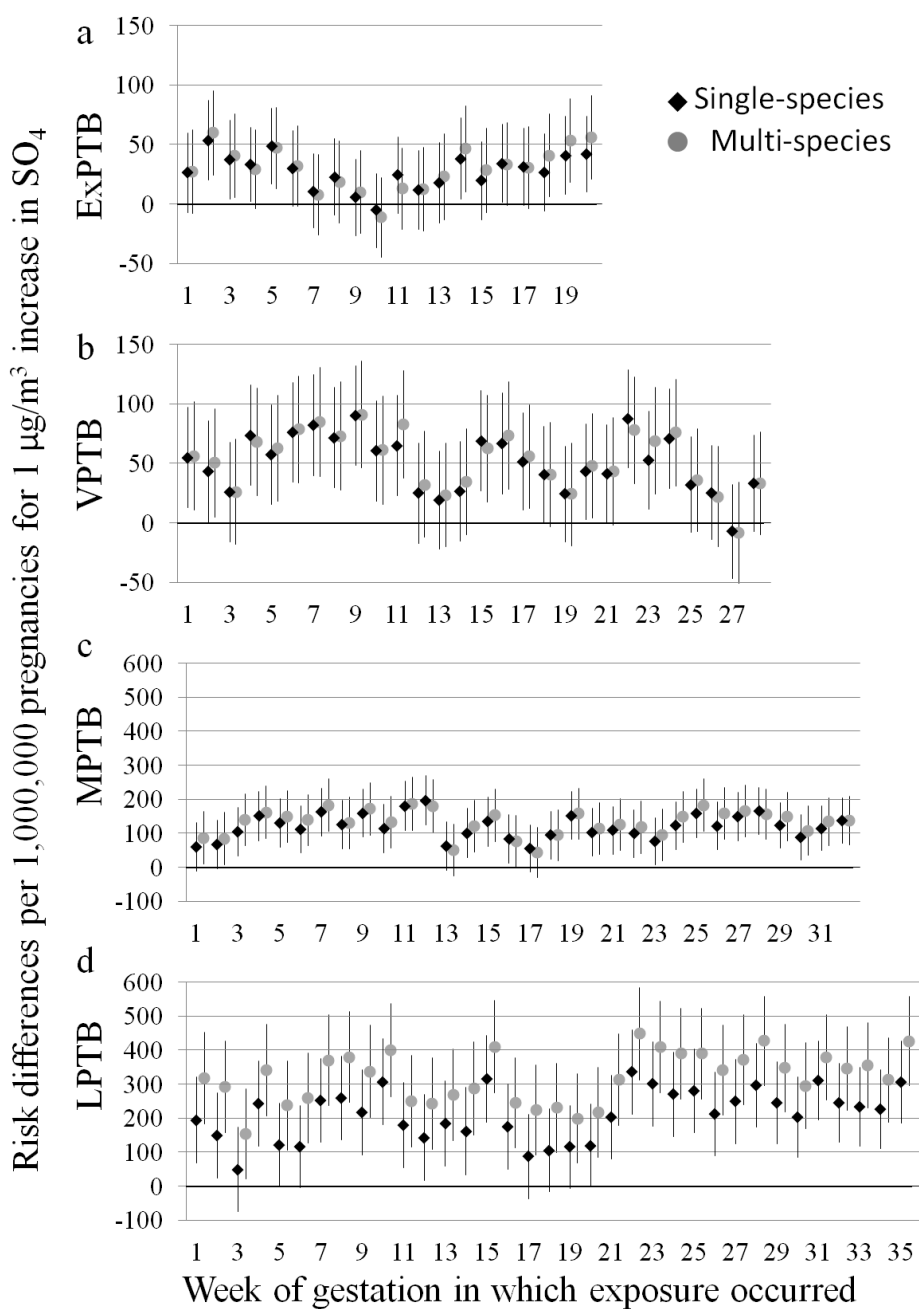


Figure 5.

